REMARKS

Amendments to the Claims

Claims 61-65 have been added and Claims 23, 25, 26, 33 and 59 have been amended to further and more particularly define that which Applicants regard as their invention.

Support for the amendments to the claims is found throughout the specification. For example, page 25, line 6 through page 26, line 2, numerical values are described indicating deleterious alleles that interfere with reproduction; page 23, lines 10-21 describe allele frequencies as would be expected if alleles were causative or preventative of mortal disease. In addition, the example starting on page 131, line 16, describes the detection of deleterious alleles by determining the sum frequencies of all obligatory knockout point mutations. Also, the Specification is clear that the claimed invention allows for the detection of a set of all occurring point mutations in a sample (see the example on page 36, line 12, through page 38, line 2).

Support for the new claims can be found, for example, on page 25, line 6 through page 26, line 2, where numerical values are described indicating deleterious alleles that interfere with reproduction, and in the example starting on page 131, line 16.

No new matter has been added. Entry of the amendments to the claims is respectfully requested.

Rejection of Claims 23, 25-28, 33, 59 and 60 under 35 U.S.C. §112, second paragraph

The Examiner rejects Claims 23, 25-28, 33, 59 and 60 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention.

Applicants have amended Claims 23, 25, 26, 33 and 59 to obviate rejections A, B, F, G, L O, P, R, T, U and V as listed in the Office Action. Applicants note that although Claims 27 and 28 were rejected, the Examiner did not indicate any indefinite phrases of these particular Claims.

With respect to rejections C, D, E, H, I, J, K, P, S, U and Y, as listed in the Office Action, Applicant respectfully disagrees with the Examiner that these rejections represent indefiniteness. In each of these rejections, a definite and unique quantity, frequency or set is referred to. For example, in determining 'the frequencies' of particular point mutations, a definite frequency,

expressed as a number is contemplated. It is not 'a frequency' at which a given mutation occurs, but rather 'the frequency'- a definite and measurable number. Any particular point mutations occurs at a specific frequency in a population. It would not be appropriate to suggest that the frequency at which a particular point mutation occurs in a population is variable. It is a determinable and unique number. Likewise, the 'set of all inherited point mutations occurring at a frequency at or above 5×10^{-5}' is a unique set. This is not an indefinite term within the context of 35 U.S.C. 112, second paragraph, because a unique set is referred to. Likewise, the terms, "the sum of the frequency", "the age -specific decline" and "the mutant fraction", each represent unique and determinable mathematical values. Therefore, since the language that is definite because it describes unique and definite quantities, frequencies and sets, reconsideration and withdrawal of these rejections are respectfully requested.

With respect to rejection M, the Applicant refers to the Specification where the phrase is defined. For example, on page 22, lines 7-11, it is stated, "'significant' means statistically significant. Statistical significance can be determined using a suitable statistical test, such as Chi square test or multinomial distribution, modified to account for the fact that a large number of alleles are being compared. For example, the statistical test can be modified by application of the Bonferoni inequality."

With respect to rejection N, Claim 26 has been amended to obviate the rejection.

In light of Applicant's remarks and amendments, reconsideration and withdrawal of rejections A through Y are respectfully requested.

Rejection of Claims 25, 33 and 59 under 35 U.S.C. §102(b)

The Examiner rejects Claims 25, 33 and 59 under 35 U.S.C. §102(b) as being anticipated by Kervinen *et al.* (1994, *Atherosclerosis*, 105:89-95).

The Applicant respectfully disagrees. In order for a reference to anticipate a claim under 35 U.S.C. 102, the reference must teach every aspect of the claimed invention either explicitly or impliedly. (MPEP 706.02). The teachings of Kervinen *et al.* do not teach identification of the set of harmful point mutations that occur at about or above a frequency of 10^{-5}. Instead, the teaching of Kervinen *et al.* describe a few selected alleles that had been previously identified. Therefore, as this aspect of the present invention was not contemplated by the teachings of Kervinen *et al.*,

Claims 25, 33 and 59, as amended, are not anticipated by the teachings of Kervinen *et al.*
Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 60 under 35 U.S.C. §103(a)

The Examiner rejects Claim 60 under 35 U.S.C. §103(a) as being unpatentable over
Kervinen *et al.* (above) in view of Khrapko *et al.* (*Nucl. Acids Res.*, 22:364-369). The Examiner
states, "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time of
the invention to have used the point mutation detection method of Khrapko et al. (1) and (2) in
the method of mutation detection of Kervinen et al." Page 8 of the Office Action.

The Applicant respectfully disagrees. The Applicant notes that the teachings of Kervinen
et al. and Khrapko *et al.* were disclosed in 1994. As there is a tremendous need and pressure
driving the identification of deleterious alleles, if the combination of methods were obvious,
Khrapko *et al.* or Kervinen *et al.* certainly could and would have conceived of Applicant's
invention. Methods at the time of filing relied on the fortuitous identification of different alleles,
followed by an analysis of whether or not the alleles had a deleterious effect. In the face of the
status quo as such, the notion that huge populations, relative to what skilled artisans were capable
of before the time of filing, of molecules could be screened was revolutionary and far from
obvious. As pointed out above, skilled artisans methodically identified polymorphisms, usually
through sequencing- an approach that merely identifies differences. The identification of
polymorphisms via these methods was extraordinarily slow and did not provide any information
as to whether the polymorphisms were significant with respect to disease. The significance of
each polymorphism had to be determined after identification of the allele. Until Applicant's
unexpected finding that large populations of alleles can be screened, skilled artisans knew only
how to identify polymorphisms first and then examine the identified polymorphisms to determine
whether or not they are deleterious. Unexpectedly, the Applicant demonstrated that one need not
identify specific polymorphisms first if one is capable of screening large populations of alleles
(*e.g.*, populations that contain rare alleles).

Given the knowledge of the skilled artisan at the time of filing, the lack of any group
contemplating or developing Applicant's invention subsequent to the disclosure of the teachings
of Khrapko *et al.* and Kervinen *et al.* despite enormous pressure from the utility of such an

invention, and the disclosure of the Applicant's unexpected findings that harmful point mutations can be identified without first knowing which particular alleles to focus in on, the Applicant argues that the invention claimed in Claim 60 was not obvious at the time of filing. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By _____
Doreen M. Hogle
Registration No.: 36,361
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

23.   (Amended) A method for identifying genes that [which] carry one or more [a] harmful allele, comprising:

    a)   identifying one or more [the] inherited point mutations that [which] are found in one or more [the] genes or portions thereof of a population of young individuals, determining the frequency [frequencies] with which each point mutation occurs, and calculating the sum of the frequencies [frequency] of all point mutations identified for each gene or segment;

    b)   identifying one or more [the] inherited point mutations that [which] are found in one or more [the] genes or portions thereof of a population of aged individuals, determining the frequency [frequencies] with which each point mutation occurs, and calculating the sum of the frequencies of all point mutations identified for each gene or segment;

    c)   comparing the sum of the frequencies [frequency] of point mutations that [which] are found in a selected gene or portion thereof of the young population calculated in a) with the sum of the frequencies [frequency] of point mutations that [mutation which] are found in the same gene or portion thereof of the aged population calculated in b), wherein a significant decrease in the sum of the frequencies [frequency] of point mutations in the aged population indicates that said selected gene carries one or more [a] harmful allele.

25.   (Twice Amended) A method for identifying genes that [which] carry a harmful allele, comprising:

    a)   identifying the set of inherited point mutations that [which] are found in one or more [the] genes or portions thereof of a population of young individuals, wherein the set comprises [of] all inherited point mutations occurring at a frequency at about or above

5×10^{-5} [can be identified], and determining the <u>frequency</u> [frequencies] with which each point mutation occurs;

b)   identifying the set of inherited point mutations <u>that</u> [which] are found in the genes or portions thereof of a population of aged individuals, and determining the frequency with which each point mutation occurs; and

c)   comparing the frequency of each point mutation identified in a selected gene or portion thereof of the young population determined in a) with the frequency of the same point mutations identified in said selected gene of the aged population determined in b), wherein a significant decrease in the frequency of two or more point mutations in said selected gene of the aged population relative to said selected gene of the young population indicates that said selected gene carries a harmful allele.

26.   (Amended)The method of Claim 25 further comprising:

d)   determining the frequency of said two or more point mutations <u>that</u> [which] decrease in the aged population in said selected gene of one or more intermediate age-specific populations;

e)   determining the age-specific <u>decrease</u> [decline] of said two or more point mutations; and

f)   comparing the age-specific <u>decrease in frequency</u> [decline] determined in e) with the expected age-specific <u>decrease in frequency</u> [decline] of a set of harmful alleles <u>that</u> [which] cause a particular mortal diseases, and determining if the functions are significantly different,

wherein a determination that the age-specific <u>decrease in frequency</u> [decline] determined in e) is not significantly different from the <u>expected</u> [theoretical] age-specific <u>decrease in frequency</u> [decline] of harmful alleles [which cause one or more mortal diseases] further indicates that said selected gene carries a harmful allele and has a high probability of being causal of said one or more mortal diseases.

33. (Twice Amended) A method for identifying genes that [which] carry a harmful allele or that [which] are linked to a gene that carries a harmful allele, comprising:

   a) identifying the set of inherited point mutations that [which] are found in one or more [the] genes or portions thereof of a population of young individuals, wherein the set comprises [of] all inherited point mutations occurring at a frequency at about or above 5×10^{-5} [can be identified], and determining the frequency [frequencies] with which each point mutation occurs;

   b) identifying the set of inherited point mutations that [which] are found in the genes or portions thereof of a population of aged individuals, and determining the frequency with which each point mutation occurs;

   c) comparing the frequency of each point mutation identified in a selected gene or portion thereof of the young population determined in a) with the frequency of the same point mutations identified in said selected gene of the aged population determined in b), wherein a significant decrease in the frequency of a point mutation in said selected gene of the aged population relative to said selected gene of the young population indicates that said selected gene carries a harmful allele or is linked to a gene that carries a harmful allele.

59. (Amended) A method of identifying one or more [the] inherited point mutations in any target region of a genome of a population, wherein said point mutations

   [a] interfere with reproduction;

   b)] cause or accelerate the appearance of a mortal disease[;] or

   [c)] prevent or delay the appearance of a mortal disease,[;]

   comprising:

   a) determining [wherein] the set of all inherited point mutations occurring at a frequency at or above 5×10^{-5} [is first identified] separately in members of the same population that comprises [who comprise] subpopulations selected from the group consisting of young, aged, intermediate age, afflicted with disease, afflicted with a disease of early age onset and afflicted with a disease of late age onset; and

b) [, by noting] <u>determining</u> the frequencies of each inherited point mutation within and between the subpopulations,

<u>wherein a decrease in the frequency in the aged population is indicative of an allele that causes or accelerates a mortal disease, and an increase in frequency in the intermediate or aged population is indicative of an allele that prevents or delays the appearance of a mortal disease</u> [thereby determining which inherited point mutations are deleterious, harmful or beneficial].